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**DESCRIPTION****METHOD OF ENANTIOSELECTIVE NUCLEOPHILIC ADDITION  
REACTION OF ENAMIDE TO CARBONYL GROUP AND  
SYNTHESIS METHOD OF OPTICALLY ACTIVE  
 $\alpha$ -HYDROXY- $\gamma$ -KETO ACID ESTER AND HYDROXYDIKETONE****Technical Field**

The present invention relates to a method of an enantioselective nucleophilic addition reaction of enamide to a carbonyl group which enables an asymmetric synthesis of an optically active compound which is useful as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like and, as an application thereof, a synthesis method of an optically active  $\alpha$ -hydroxy- $\gamma$ -keto acid ester, hydroxydiketone or the like.

**Background Art**

Conventionally, a method of a nucleophilic addition reaction to an aldehyde group of an aldehyde compound or an imino group of an imine compound derived from the aldehyde compound has been studied and, in recent years, this nucleophilic addition reaction has drawn attention as a measure for efficiently and asymmetrically synthesizing an amino acid derivative, a hydroxycarboxylic acid or the like as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like.

Under these circumstances, the present inventors have developed and disclosed a method for synthesizing an N-acylated amino acid derivative by a nucleophilic addition reaction to an N-acylimino ester compound by using a polymer-carrying catalyst (Journal of Combinatorial Chemistry, 2001, Vol. 3, No. 5, 401 to 403) and, further, a method for enantioselectively synthesizing these compounds by using a chiral copper catalyst (Org. Lett. Vol. 4, No. 1, 2002, 143 to 145; J. Am. Chem. Soc. Vol. 125, No. 9, 2003, 2507 to 2515).

However, the nucleophilic addition reaction on which the present inventors have studied is limited to such nucleophilic reactants as a silyl enol

ether and an alkyl vinyl ether and, accordingly, a subject to which the nucleophilic addition reaction is applied and such application thereof have inevitably been restricted.

Then, under these circumstances, the present invention has an object of providing a method of an enantioselective nucleophilic addition reaction to a carbonyl group which enables an asymmetric synthesis of an  $\alpha$ -hydroxy- $\gamma$ -keto acid compound, an  $\alpha$ -hydroxy- $\gamma$ -amino acid compound or the like which is useful as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like and, further, as an application thereof, a novel synthesis method of the  $\alpha$ -hydroxy- $\gamma$ -keto acid ester or the like.

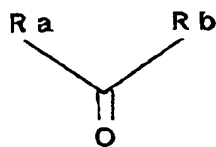
#### Disclosure of Invention

In order to solve these problems, according to a first aspect of the present invention, there is provided a method of an enantioselective nucleophilic addition reaction of enamide which is a method of a nucleophilic addition reaction of an enamide compound accompanied by generation of a hydroxyl group (-OH) to a carbonyl group and which is characterized by allowing the reaction to be performed in the presence of a chiral catalyst containing copper or nickel.

Then, with reference to the above-described method, according to a second aspect of the invention, there is provided the method of the enantioselective nucleophilic addition reaction of enamide which is characterized in that the chiral catalyst is constituted by a copper compound or a nickel compound which is a salt of an organic or inorganic acid or a complex or composite of the salt, and a chiral diamine ligand and, according to a third aspect of the invention, there is provided the method of the enantioselective nucleophilic addition reaction of enamide which is characterized in that the chiral diamine ligand has an ethylene diamine structure as a portion thereof.

Further, according to a fourth aspect of the invention, with reference to the above-described method, there is provided the method of the enantioselective nucleophilic addition reaction of enamide which is characterized in that a nucleophilic addition reaction of an enamide compound accompanied by

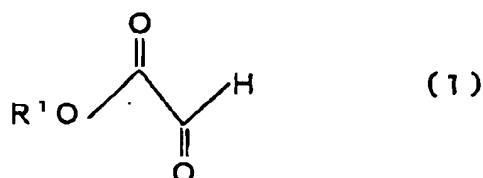
generation of a hydroxyl group (-OH) to a carbonyl group is performed on a compound having a carbonyl group represented by the following formula:



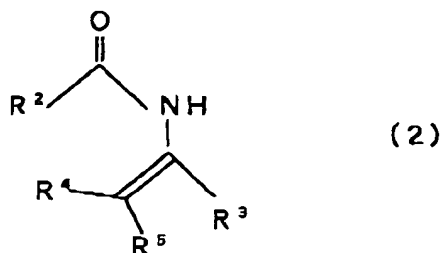
(wherein Ra represents a hydrocarbon group which may have a substituent, R<sup>0</sup>-CO- or R<sup>0</sup>-O-CO-, wherein R<sup>0</sup> represents a hydrocarbon group which may have a substituent; and

Rb represents a hydrogen atom or a hydrocarbon group which may have a substituent).

According to a fifth aspect of the invention, there is provided the method of the enantioselective nucleophilic addition reaction of enamide which is characterized in that the compound having the carbonyl group is a glyoxylic acid ester and, according to a sixth aspect of the invention, there is provided the method which is characterized in that an aldehyde compound is a glyoxylic acid ester represented by the following formula (1):



(wherein R<sup>1</sup> represents a hydrocarbon group which may have a substituent; and the enamide compound is represented by the following formula (2):



(wherein R<sup>2</sup> represents a hydrocarbon group which may have a

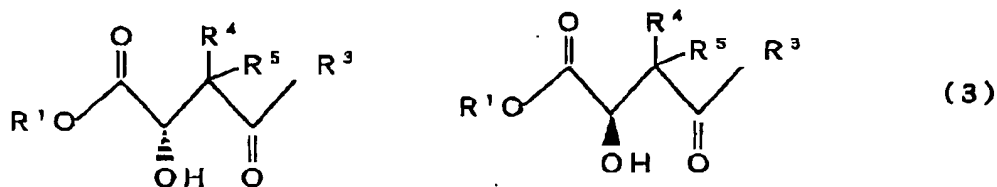
substituent or a hydrocarbon group which may have a substituent to be bonded via an oxygen atom;

$R^3$  represents a hydrocarbon group which may have a substituent;

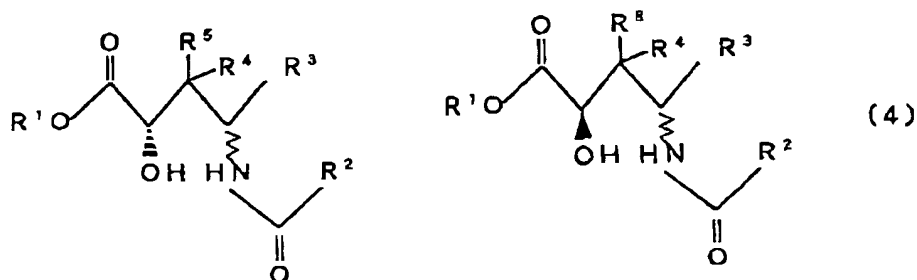
$R^4$  and  $R^5$  may be same with or different from each other and each represent a hydrogen atom or a hydrocarbon group which may have a substituent, wherein at least one of them represents a hydrogen atom; and

$R^3$  may form a ring by being bonded with  $R^4$  or  $R^5$ .

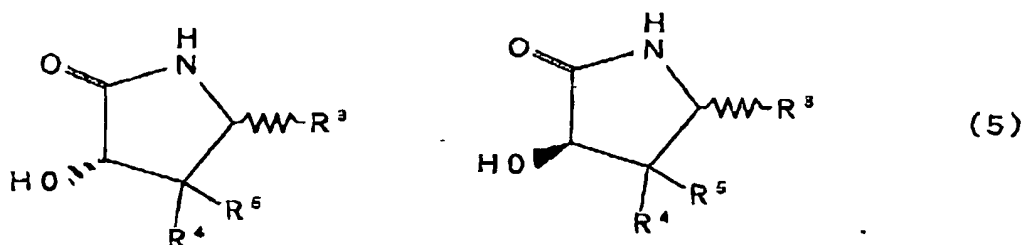
According to a seventh aspect of the invention, there is provided a method for synthesizing an optically active  $\alpha$ -hydroxy- $\gamma$ -keto acid ester which is characterized in that, after the above-described nucleophilic addition reaction, an acid treatment is performed, to thereby generate a compound represented by at least one of the following formulae (3):



(wherein  $R^1$ ,  $R^3$ ,  $R^4$  and  $R^5$  each represent same article as described above) and, according to an eighth aspect of the invention, there is provided a method for synthesizing an optically active  $\alpha$ -hydroxy- $\gamma$ -amino acid ester which is characterized in that, after the above-described nucleophilic addition reaction, a reduction treatment is performed, to thereby generate a compound represented by at least one of the following formulae (4):

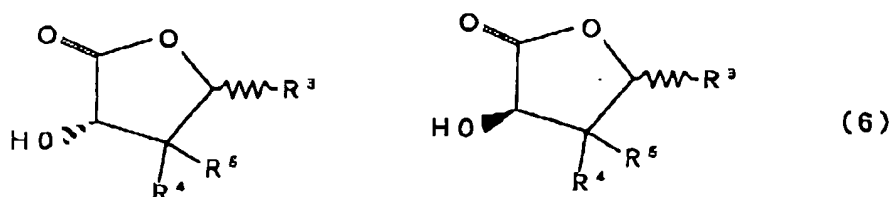


(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  each represent same article as described above) and, further, according to a ninth aspect of the invention, there is provided a method for synthesizing any one of optically active  $\alpha$ -hydroxy- $\gamma$ -lactams which is characterized in that, after a substituent ( $R^2CO-$ ) on a  $\gamma$ -amino group of the thus-synthesized optically active  $\alpha$ -hydroxy- $\gamma$ -amino acid ester is removed, a cyclization reaction is performed, to thereby generate a compound represented by at least one of the following formulae (5):



(wherein  $R^3$ ,  $R^4$  and  $R^5$  each represent same article as described above).

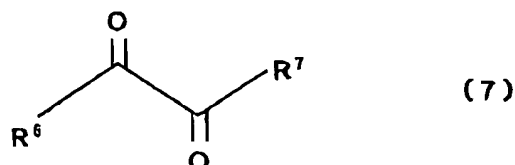
Still further, according to a tenth aspect of the invention, there is provided a method for synthesizing any one of optically active  $\alpha$ -hydroxy- $\gamma$ -lactones which is characterized in that the optically active  $\alpha$ -hydroxy- $\gamma$ -keto acid ester synthesized by the above-described seventh aspect of the invention is subjected to a reduction reaction and, subsequently, to a cyclization reaction, to thereby generate a compound represented by at least one of the following formulae (6):



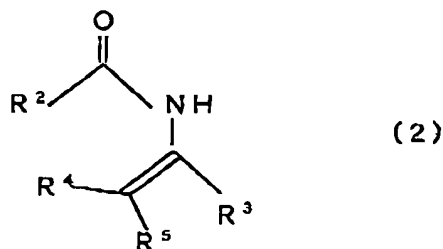
(wherein  $R^3$ ,  $R^4$  and  $R^5$  each represent same article as described above).

Then, according to an eleventh aspect of the invention, there is provided a method of an enantioselective nucleophilic addition reaction of enamide which is the enantioselective nucleophilic addition reaction of enamide according to the

fourth aspect of the invention and which is characterized in that the compound having the carbonyl group is a diketone compound represented by the following formulae (7):



(wherein  $\text{R}^6$  and  $\text{R}^7$  are same with or different from each other and each represent a hydrocarbon group which may have a substituent); and  
the enamide compound is represented by the following formula (2):



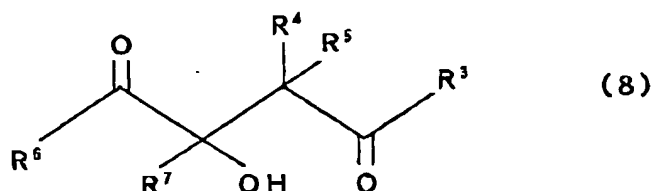
(wherein  $\text{R}^2$  represents a hydrocarbon group which may have a substituent or a hydrocarbon group which may have a substituent to be bonded via an oxygen atom;

$\text{R}^3$  represents a hydrocarbon group which may have a substituent;

$\text{R}^4$  and  $\text{R}^5$  may be same with or different from each other and each represent a hydrogen atom or a hydrocarbon group which may have a substituent, wherein at least one of them represents a hydrogen atom; and

$\text{R}^3$  may form a ring by being bonded with  $\text{R}^4$  or  $\text{R}^5$ ).

According to a twelfth aspect of the invention, there is provided a method for synthesizing an optically active hydroxydiketone compound which is characterized in that, after this nucleophilic addition reaction, an acid treatment is performed, to thereby generate an optical active compound represented by the following formula (8):



(wherein  $R^6$ ,  $R^7$ ,  $R^3$ ,  $R^4$  and  $R^5$  each represent same article as described above).

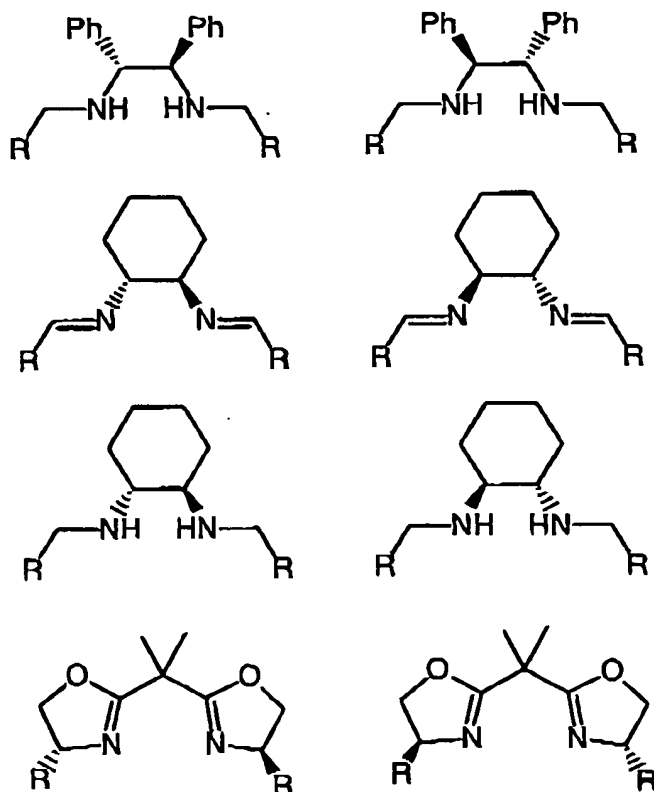
### Best Mode for Carrying Out the Invention

The present invention has characteristics as described above and is, further, described with reference to embodiments thereof.

In a method of an enantioselective nucleophilic addition reaction of enamide to a carbonyl group according to the invention, a chiral copper catalyst or a chiral nickel catalyst is used as a catalyst. As for the chiral catalyst on this occasion, various types of such chiral catalysts in each of which a copper (Cu) or nickel (Ni) atom is indispensable for a constitution thereof and to each of which a chiral organic molecular structure is attached are considered. Ordinarily, the chiral catalyst is constituted by a copper compound or nickel compound and a chiral organic compound and, more practically, from the standpoint of reaction yield and enantioselectivity, the chiral catalyst constituted by a copper compound or nickel compound and a chiral diamine ligand compound is favorably considered. The copper compound or nickel compound may be selected from among various types of salts, complex salts, organic metal compounds and the like as a monovalent or bivalent compound and, among other things, a salt with an organic or inorganic acid, a complex or organic composite of the salt is favorably mentioned. Among these compounds, a salt with a strong acid, for example, a salt of (per)fluoroalkyl sulfonic acid, perchloric acid or sulfonic acid, a complex or an organic composite of the salt is favorably illustrated. For example,  $\text{Cu}(\text{OTf})_2$ ,  $\text{CuClO}_4$ ,  $\text{CuClO}_4 \cdot 4\text{CH}_3\text{CN}$ ,  $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{Ni}(\text{OTf})_2$ , and  $\text{NiX}_2 + \text{AgOTf}$  (X being a halogen atom) are mentioned.

As for the chiral diamine ligand as a counterpart, an article having an ethylene diamine structure in a molecular constitution as a portion thereof is

favorably used. On this occasion, an amino group may contain an imine bond. For example, as representatives, various types represented by the following formulae are illustrated:



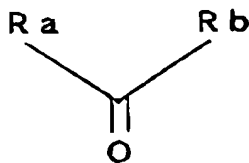
On this occasion, R in the formulae represents a hydrocarbon group which may have a substituent. The hydrocarbon group may be any one of various types in a chain state or a cyclic state and may have, as a substituent, a halogen atom, a hydrocarbon group of an alkyl group or the like, an alkoxy group or the like. Further, Ph (phenyl group) and a cyclohexyl group in the formulae may each have a substituent.

With reference to the chiral catalyst containing copper or nickel as described above according to the invention, a complex may previously be prepared by using a copper compound or a nickel compound and a chiral organic molecule and, then, used as a catalyst, or the copper compound or the nickel compound and the chiral organic molecule may be mixed with each other in a reaction system and, then, used. As far as a ratio in use as a catalyst is



concerned, the copper compound or nickel compound or the complex of the copper compound or nickel compound and the chiral organic molecule is used at a rate of ordinarily from about 0.5 to about 30% by mol against the carbonyl compound.

The carbonyl compound to be used in the reaction may have any type of structure of an aliphatic, alicyclic, aromatic or a heterocyclic carbonyl compound or the like which may have a substituent, so long as it does not interfere with the nucleophilic addition reaction according to the present invention. For example, such carbonyl compound as described above may be the compound having the carbonyl group represented by the following formula as described above:



(wherein Ra represents a hydrocarbon group which may have a substituent,  $R^0$ -CO- or  $R^0$ -O-CO-, wherein  $R^0$  represents a hydrocarbon group which may have a substituent; and

Rb represents a hydrogen atom or a hydrocarbon group which may have a substituent).

For example, as for the compound having a carbonyl group, a glyoxylic acid ester represented by the formula (1) is illustrated. This article has an ester bond portion and reference mark  $R^1$  in the formula represents a hydrocarbon group which may have a substituent. The hydrocarbon group may be any one of various types of hydrocarbon groups, for example, a chain or an alicyclic hydrocarbon group, an aromatic hydrocarbon group and mixtures thereof. As for such substituents, so long as they do not interfere with the nucleophilic addition reaction, the hydrocarbon group may appropriately have any one of various types of substituents such as a hydrocarbon group such as an alkyl group, an alkoxy group, a sulfide group, a cyano group, a nitro group, and an ester group.

The enamide compound as a counterpart can, for example, be

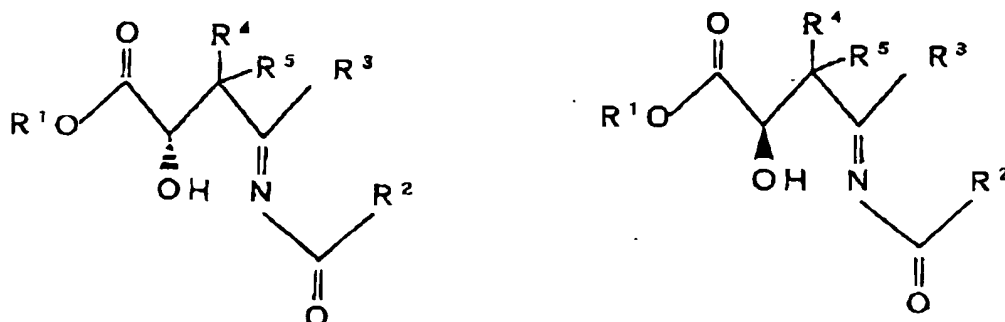
represented by the above-described formula (2). As for characteristics thereof, it has an amide bond or a carbamate bond. As for reference marks in the formula,  $R^2$  represents a hydrocarbon group which may have a substituent or a hydrocarbon group which may have a substituent to be bonded via an oxygen atom;  $R^3$  represents a hydrocarbon group which may have a substituent; and  $R^4$  and  $R^5$  may be same with or different from each other and each represent a hydrogen atom or a hydrocarbon group which may have a substituent, in which at least one of them represents a hydrogen atom.

The hydrocarbon group may be any one of various types of hydrocarbon groups in a same manner as described above, for example, an aliphatic hydrocarbon group, an alicyclic hydrocarbon group, an aromatic hydrocarbon group and mixtures thereof. As for such substituents, various types of substituents such as a hydrocarbon group such as an alkyl group, a halogen atom, an alkoxy group, a sulfide group, a cyano group, a nitro group, and an ester group are appropriately be considered.

Further, as for reference mark  $R^2$ , a hydrocarbon group which is bonded via an oxygen atom such as  $-OEt$ ,  $-O^tBu$ , or  $-OBn$  is appropriately illustrated. As for reference mark  $R^3$ , an article having a substituent such as a phenyl group, a naphthyl group, or any one of these groups each having a substituent such as a halogen atom, an alkyl group, or an alkoxy group is favorably illustrated. In the nucleophilic addition reaction of the enamide compound to the aldehyde group ( $-CHO$ ) of the glyoxylic acid ester, an appropriate organic solvent, for example, a halogenated hydrocarbon, any one of nitriles such as acetonitrile, or any one of ethers such as THF may be used and, in a reaction temperature, a range of from about  $-20^{\circ}C$  to about  $40^{\circ}C$  can appropriately be adopted. A ratio of the aldehyde compound to the enamide compound to be used in an atmosphere of the air or in an inert atmosphere can appropriately be set to be in the range of from about 0.1 to about 10 in terms of a molar ratio.

In the nucleophilic addition reaction of the enamide compound, when a reaction between the glyoxylic acid ester represented by the above-described formula (1) and the enamide compound represented by the above-described formula (2) is taken as an example, an optically active  $\alpha$ -hydroxy- $\gamma$ -imino acid ester represented by at least one of the following formulae is enantioselectively

generated:



Then, particularly, when enecarbamate is used as a type of the enamide compound, a high stereoselectivity can also be realized. A syn-adduct and an anti-adduct can be obtained from a Z-body and an E-body at high diastereoselectivity and high enantioselectivity, respectively. By either without isolating or isolating the above-described imino acid ester compound, an acid treatment, for example, an acid treatment by using an aqueous solution of HCl, HBr or the like is performed, to thereby obtain the optically active  $\alpha$ -hydroxy- $\gamma$ -keto acid ester represented by the above-described formula (3) at high yield and with excellent enantioselectivity.

Further, on the other hand, without performing the acid treatment but performing a reduction treatment, the optically active  $\alpha$ -hydroxy- $\gamma$ -amino acid ester represented by the above-described formula (4) can be obtained at high yield and with excellent enantioselectivity in a same manner as described above. The reduction treatment on this occasion can use, for example, a boron reducing agent compound such as  $\text{Et}_2\text{BOMe-NaBH}_4$ , any one of other metal hydrides or a metallic hydrogen complex compound. Then, the thus-generated optically active  $\alpha$ -hydroxy- $\gamma$ -amino acid ester is subjected to a cyclization reaction to remove an acyl group on a  $\gamma$ -amino group therefrom (freeig from protection), to thereby being favorably converted into any one of optically active  $\alpha$ -hydroxy- $\gamma$ -lactams represented by the formula (5). For example, when the acyl group is a benzyloxycarbonyl group, protection freeing-cyclization reaction can be performed by catalytic hydrogen reduction.

Further, in the present invention, it is possible to synthesize the optically active  $\alpha$ -hydroxy- $\gamma$ -lactams as represented by the above-described formula (6) by

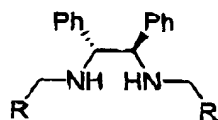
subject the optically active  $\alpha$ -hydroxy- $\gamma$ -keto acid ester as described above firstly to a reduction reaction and, then, to a cyclization reaction.

Then, in the present invention, it is illustrated as a favorable example that a compound having a carbonyl group is a diketone compound as is represented by the above-described formula (7). Reference marks  $R^6$  and  $R^7$  in the formula (7) may be various types of hydrocarbon groups in a same manner as described above. It is possible to synthesize an optically active hydroxydiketone compound as shown in the formula (8) by performing the nucleophilic addition reaction of the enamide compound of the formula (2) on this diketone compound.

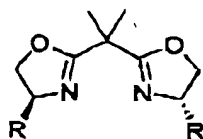
Hereinafter, the present invention is described in detail with reference to embodiments. It goes without saying that the present invention is not limited to these embodiments.

## EXAMPLES

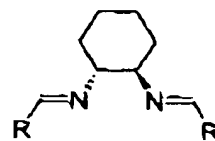
In Examples described below, unless stated otherwise, reference numerals and marks of chiral diamine ligands are denoted as follows:



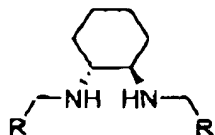
- 3a: R = 1-nap  
 3b: R = (3,5- $t$ Bu)<sub>2</sub>-Ph  
 3c: R =  $t$ Bu  
 3d: R = Ph  
 3e: R = (o-F)-Ph  
 3f: R = (o-OMe)-Ph



- 3g: R = Ph  
 3h: R =  $t$ Bu



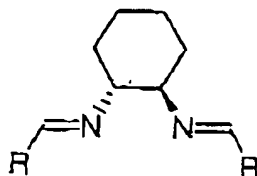
- 3i: R = Ph  
 3j: R = 1-nap  
 3k: R = 2-nap  
 3l: R = (3,5-di $t$ Bu)-C<sub>6</sub>H<sub>3</sub>  
 3m: R = o-Tol  
 3n: R = *m*-Tol  
 3o: R = *p*-Tol  
 3p: R = *p*-Et-C<sub>6</sub>H<sub>4</sub>  
 3q: R = *p*-Pr-C<sub>6</sub>H<sub>4</sub>  
 3r: R = *p*-F-C<sub>6</sub>H<sub>4</sub>  
 3s: R = *p*-Cl-C<sub>6</sub>H<sub>4</sub>  
 3t: R = *p*-Br-C<sub>6</sub>H<sub>4</sub>



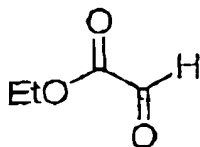
- 3v: R = Ph  
 3w: R = 2-nap  
 3x: R = (3,5- $t$ Bu)<sub>2</sub>-Ph

## &lt;Example 1&gt;

In the formula described below, a  $\text{CH}_2\text{Cl}_2$  (1.5 ml) solution of chiral diamine ligand (9.9 mg, 0.022 mmol) in which R represents  $4\text{-BrC}_6\text{H}_4$  is added to  $\text{CuClO}_4 \cdot 4\text{CH}_3\text{CN}$  (6.5 mg, 0.020 mmol) in an argon atmosphere and the resultant excellent yellow solution was stirred for 8 hours or more and, then, cooled to  $0^\circ\text{C}$ .



Next, into the resultant mixed solution, a  $\text{CH}_2\text{Cl}_2$  (0.8 ml) solution of ethyl glyoxylate (100  $\mu\text{l}$ , 0.40 mmol) represented by the formula described below was added and, further, a  $\text{CH}_2\text{Cl}_2$  (0.8 ml) solution of enamide (0.20 mmol) represented by the formula (2) as shown in Table 1 was added.



The resultant reaction mixed solution was stirred for one hour at  $0^\circ\text{C}$  and, then, added with a saturated aqueous solution of  $\text{NaHCO}_3$ , to thereby terminate a reaction. Thereafter, the resultant reaction mixed solution was allowed to have room temperature and, then, subjected to extraction by using  $\text{CH}_2\text{Cl}_2$ . The resultant organic phase was rinsed and, then, dried. After a solvent was evaporated, a residue was dissolved in EtOH (3.0 ml), added with a 48% aqueous HBr solution (0.3 ml) and, then, stirred for 1.5 minute at room temperature.

The resultant reaction mixture was subjected to extraction by using  $\text{CH}_2\text{Cl}_2$ . The resultant organic phase was rinsed and, then, dried. After a solvent was evaporated, a crude product was obtained. This crude product was purified by using silica gel chromatography.

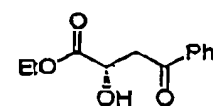
In Table 1, the reaction yield and ee (%) in accordance with the type of enamide are shown. On this occasion, the ee (%) was determined by an HPLC

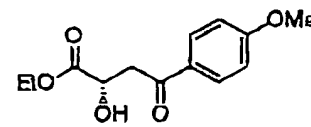
analysis.

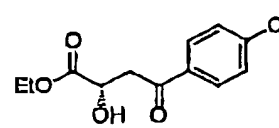
**Table 1**

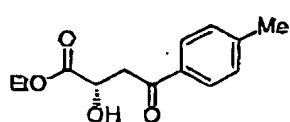
No.	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup> , R <sup>5</sup>	Yield (%)	ee (%)
1-1	BnO	Ph	H, H	93	97
1-2	BnO	4-MeO-Ph	H, H	94	93
1-3	BnO	4-Cl-Ph	H, H	97	97
1-4	BnO	4-Me-Ph	H, H	quantum	96
1-5	BnO	2-naphthyl	H, H	91	96

Identification values of products in the case of Nos. 1-1 to 1-5 are shown below.

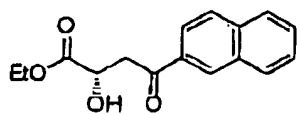

**(2S)-2-Hydroxy-4-oxo-4-phenyl-butyrac acid ethyl ester:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 1.27 (t, 3H,  $J$  = 7.1 Hz), 3.29 (brs, 1H), 3.44 (dd, 1H,  $J$  = 6.1, 17.6 Hz), 3.52 (dd, 1H,  $J$  = 3.9, 17.6 Hz), 4.25 (q, 2H,  $J$  = 7.1 Hz), 4.61-4.67 (m, 1H), 7.44-7.50 (m, 2H), 7.54-7.60 (m, 1H), 7.92-7.98 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 14.0, 42.1, 61.8, 67.1, 128.1, 128.6, 133.5, 136.4, 173.7, 197.5. IR (neat) 3475, 3063, 2983, 1737, 1687, 1597, 1580, 1449, 1368, 1213, 1098, 1045, 860, 759, 690, 582, 499  $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{12}\text{H}_{15}\text{O}_4$   $[\text{M}+\text{H}]^+$ , 223.0970. Found 223.0972.; HPLC, Daicel Chiralcel ADH, hexane/ $i$ PrOH = 4/1, flow rate = 0.5 mL/min :  $t_R$  = 19.9 min (S),  $t_R$  = 22.2 min (R).


**(2S)-2-Hydroxy-4-(4-methoxy-phenyl)-4-oxo-butyrac acid ethyl ester:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 1.28 (t, 3H,  $J$  = 7.1 Hz), 3.41 (dd, 1H,  $J$  = 5.9, 17.4 Hz), 3.48 (dd, 1H,  $J$  = 4.0, 17.4 Hz), 3.48 (brd, 1H,  $J$  = 6.8 Hz), 3.87 (s, 3H), 4.26 (q, 2H,  $J$  = 7.1 Hz), 4.60-4.70 (m, 1H), 6.91-6.97 (m, 2H), 7.90-7.97 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 14.0, 41.7, 55.4, 61.7, 67.3, 113.8, 129.5, 130.4, 163.8, 173.8, 196.1. IR (neat) 3483, 2979, 2841, 1739, 1677, 1600, 1575, 1512, 1465, 1421, 1368, 1265, 1172, 1099, 1027, 988, 895, 834, 737, 579  $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{13}\text{H}_{17}\text{O}_5$   $[\text{M}+\text{H}]^+$ , 253.1076. Found 253.1097.; HPLC, Daicel Chiralcel ADH, hexane/ $i$ PrOH = 4/1, flow rate = 0.4 mL/min :  $t_R$  = 43.1 min (S),  $t_R$  = 45.7 min (R).


**(2S)-4-(4-Chloro-phenyl)-2-hydroxy-4-oxo-butyrac acid ethyl ester:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 1.28 (t, 3H,  $J$  = 7.1 Hz), 3.42 (dd, 1H,  $J$  = 6.1, 17.3 Hz), 3.49 (dd, 1H,  $J$  = 3.9, 17.3 Hz), 3.41-3.47 (brd, 1H), 4.26 (q, 2H,  $J$  = 7.1 Hz), 4.62-4.70 (m, 1H), 7.42-7.48 (m, 2H), 7.86-7.93 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 14.1, 42.2, 62.0, 67.1, 129.0, 129.6, 134.8, 140.1, 173.7, 196.3. IR (neat) 3480, 2982, 1739, 1684, 1590, 1573, 1402, 1213, 1093, 1045, 820, 531  $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{12}\text{H}_{14}\text{ClO}_4$   $[\text{M}+\text{H}]^+$ , 257.0580. Found 257.0584.; HPLC, Daicel Chiralcel ADH, hexane/ $i$ PrOH = 4/1, flow rate = 0.5 mL/min :  $t_R$  = 24.2 min (S),  $t_R$  = 26.5 min (R).



**(2S)-2-Hydroxy-4-oxo-4-p-tolyl-butyric acid ethyl ester:**  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  = 1.28 (t, 3H,  $J$  = 7.1 Hz), 2.41 (s, 3H), 3.44 (dd, 1H,  $J$  = 5.9, 17.4 Hz), 3.51 (dd, 1H,  $J$  = 4.0, 17.4 Hz), 3.45-3.55 (brs, 1H), 4.26 (q, 2H,  $J$  = 7.1 Hz), 4.66 (dt, 1H,  $J$  = 4.2, 5.5 Hz), 7.26 (apparent d, 2H,  $J$  = 8.0 Hz), 7.85 (apparent d, 2H,  $J$  = 8.2 Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  = 14.0, 21.6, 42.0, 61.7, 67.2, 128.2, 129.3, 133.9, 144.4, 173.7, 197.1. IR (neat) 3483, 2981, 1742, 1682, 1606, 1405, 1365, 1212, 1098, 1044, 813, 578  $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{13}\text{H}_{17}\text{O}_4$   $[\text{M}+\text{H}]^+$ , 237.1127. Found 237.1120.; HPLC, Daicel Chiralcel ADH, hexane/ $i$ PrOH = 4/1, flow rate = 0.3 mL/min :  $t_R$  = 36.1 min (*S*),  $t_R$  = 38.2 min (*R*).



**(2S)-2-Hydroxy-4-naphthalen-2-yl-4-oxo-butyric acid ethyl ester:**  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  = 1.28 (t, 3H,  $J$  = 7.1 Hz), 3.52 (d, 1H,  $J$  = 5.9 Hz), 3.59 (dd, 1H,  $J$  = 6.1, 17.3 Hz), 3.66 (dd, 1H,  $J$  = 3.9, 17.3 Hz), 4.28 (q, 2H,  $J$  = 7.1 Hz), 4.73 (dt, 1H,  $J$  = 4.2, 5.4 Hz), 7.50-7.65 (m, 2H), 7.82-8.20 (m, 4H), 8.45 (s, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  = 14.1, 42.3, 61.9, 67.3, 123.6, 126.9, 127.8, 128.6, 128.8, 129.6, 130.2, 132.4, 133.8, 135.8, 173.9, 197.5. IR (neat) 3481, 3058, 2982, 1741, 1681, 1627, 1469, 1369, 1209, 1097, 1045, 859, 824, 749, 477  $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{16}\text{H}_{17}\text{O}_4$   $[\text{M}+\text{H}]^+$ , 273.1127. Found 273.1125.; HPLC, Daicel Chiralcel ADH, hexane/ $i$ PrOH = 4/1, flow rate = 0.5 mL/min :  $t_R$  = 27.0 min (*S*),  $t_R$  = 30.4 min (*R*).

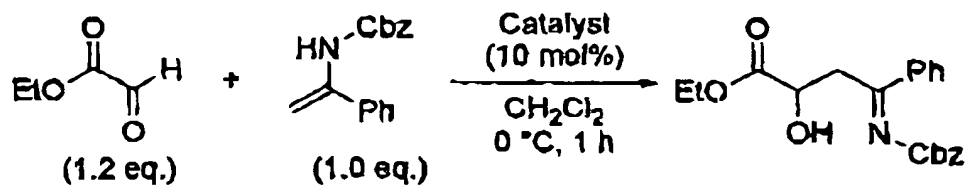
### <Example 2>

An nucleophilic addition reaction of enamide was performed by various types of chiral diamine ligands and  $\text{CuClO}_4 \cdot 4\text{CH}_3\text{CN}$ , while using No. 1-1 enamide and ethyl glyoxylate in Example 1 and, to thereby synthesize an  $\alpha$ -hydroxy- $\gamma$ -imino acid ester.

The results are shown in Table 2.



Table 2



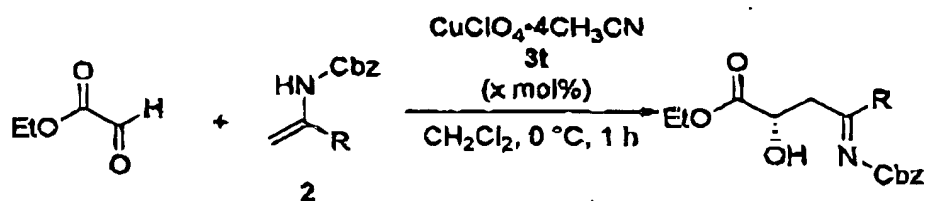
entry	metal	ligand	yield (%)	ee (%) <sup>a</sup>
1	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3a	90	35 <sup>a</sup>
2	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3i	94	93
3	CuPF <sub>6</sub> ·4CH <sub>3</sub> CN	3i	94	82
4	CuOTf·0.5C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	3l	66	78
5	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3j	92	73
6	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3k	52	68
7 <sup>b</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3l	48	91
8 <sup>c</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3i	97	93
9 <sup>d</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3l	quant	94
10 <sup>d</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3m	97	81
11 <sup>d</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3n	quant	86
12 <sup>d</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3o	98	95
13 <sup>d</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3p	87	94
14 <sup>d</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3q	93	94
15 <sup>d</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3r	97	96
16 <sup>d</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3s	93	96.5
17 <sup>d</sup>	CuClO <sub>4</sub> ·4CH <sub>3</sub> CN	3t	93	97.0

<sup>a</sup> The absolute configuration is S except in entry 1 (R). <sup>b</sup> -78 °C. <sup>c</sup> Ethyl glyoxylate (1.5 equiv) was used. <sup>d</sup> Ethyl glyoxylate (2.0 equiv) was used.

### <Example 3>

A reaction was performed in a same manner as in Example 2 except that various types of enamides were used and an amount of CuClO<sub>4</sub>·4CH<sub>3</sub>CN to be used was changed. The results are shown in Table 3. It is found that results of high yield and high ee % can be obtained even with a low concentration of a chiral copper catalyst.

Table 3



entry	<b>2</b>	$x \text{ (mol\%)}$	yield (%)	ee (%)
1	<b>2a</b> (R = Ph)	10	93	97
2	<b>2a</b>	5	94	96
3	<b>2a</b>	2	96	95
4	<b>2a</b>	1	90	94
5	<b>2b</b> (R = PMP)	10	94	93
6	<b>2c</b> (R = PCP)	10	97	97
7	<b>2d</b> (R = PMeP)	10	quant	96
8	<b>2e</b> (R = 2-Nap)	10	91	96

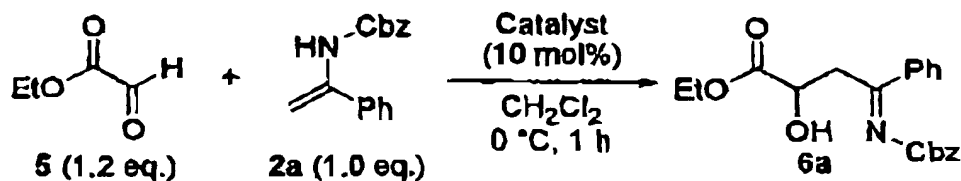
Cbz = Benzyloxycarbonyl. PMP = *p*-Methoxyphenyl.  
 PCP = *p*-Chlorophenyl. PMeP = *p*-Methylphenyl. 2-Nap  
 = 2-Naphthyl.

## &lt;Example 4&gt;

A reaction was performed in a same manner as in Example 2 except that  $\text{Cu}(\text{OTf})_2$  or the like was used in place of the copper compound.

The results are shown in Table 4. An absolute configuration of the product was R.

Table 4



entry	metal	ligand	yield (%)	ee (%) <sup>d</sup>
1	$\text{Cu}(\text{OTf})_2$	3a	93	55
2 <sup>a</sup>	$\text{Cu}(\text{OTf})_2$	3a	91	54
3 <sup>b</sup>	$\text{Cu}(\text{OTf})_2$	3a	89	58
4	$\text{Cu}(\text{OTf})_2$	3b	74	59
5	$\text{Cu}(\text{OTf})_2$	3c	58	57
6	$\text{Cu}(\text{OTf})_2$	3d	98	46
7	$\text{Cu}(\text{OTf})_2$	3e	97	37
8	$\text{Cu}(\text{OTf})_2$	3h	70	73
9	$\text{Cu}(\text{OTf})_2$	3i	65	70
10	$\text{Cu}(\text{OTf})_2$	3j	66	28
11	$\text{Cu}(\text{OTf})_2$	3k	71	52
12	$\text{Cu}(\text{OTf})_2$	3l	68	17
13	$\text{Cu}(\text{OTf})_2$	3v	89	51
14	$\text{Cu}(\text{OTf})_2$	3w	91	50
15	$\text{Cu}(\text{OTf})_2$	3x	quant	62
16	$\text{Cu}(\text{SbF}_6)_2$	3b	77	44

<sup>a</sup> Catalyst (30 mol%) was used. <sup>b</sup>  $-20^\circ\text{C}$ .

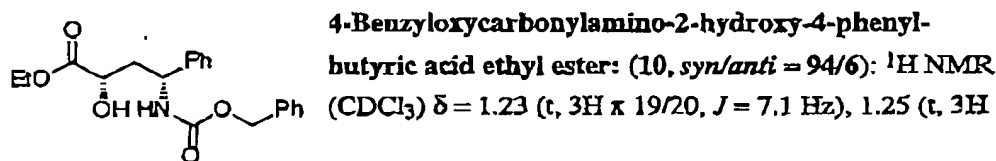
#### <Example 5>

A treatment as described below was performed in place of the acid treatment by using the aqueous HBr solution in Example 1-1.

Namely, the residue was added with a mixed solution of THF (2.0 ml) and MeOH (0.5 ml) and, then, cooled to  $-78^\circ\text{C}$  and, thereafter, added with  $\text{Et}_2\text{BOMe}$  (79  $\mu\text{l}$ , 0.6 mmol) and, subsequently, stirred for 15 minutes. The resultant mixed solution was added with  $\text{NaBH}_4$  (22.7 mg, 0.6 mmol) and, then, cooled to  $-78^\circ\text{C}$  and stirred for 2 hours at this temperature.

Then, a reaction was terminated by being added with AcOH (0.3  $\mu\text{l}$ ) and, then, allowed to have room temperature.

The compound described below was obtained in an amount of 46.5 mg at a yield of 65 %. A ratio of *syn*/*anti* was 94/6.

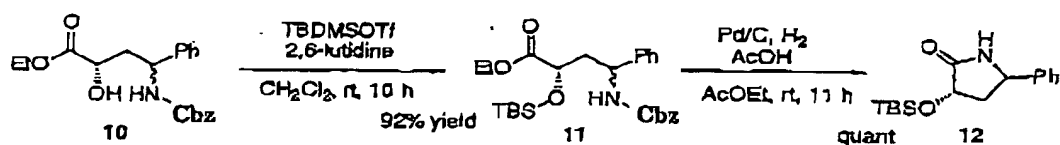


$\times$  1/20, *J* = 7.0 Hz), 1.95-2.40 (m, 2H), 3.33 (brs, 1H  $\times$  19/20), 3.51 (brs, 1H  $\times$  1/20), 4.00-4.40 (m, 3H), 4.85-5.20 (m, 3H), 5.52 (d, 1H  $\times$  19/20, *J* = 7.3 Hz), 5.96 (d, 1H  $\times$  1/20, *J* = 8.2 Hz), 7.00-7.60 (m, 10H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) *syn*: δ = 14.1, 40.3, 52.6, 61.8, 66.8, 68.4, 126.4, 127.6, 128.1, 128.4, 128.7, 136.3, 141.4, 155.7, 174.4; *anti*: (distinguishable peak) 40.2, 52.4, 67.8, 126.2, 127.4, 141.1, 156.0, 174.3; LRMS (FAB) *m/z* = 358 (*M*+H<sup>+</sup>)

In the same manner as described above, when a reaction was performed for 3 hours in the solvent of Et<sub>2</sub>O by using Zn(BH<sub>4</sub>)<sub>2</sub> (one equivalent), the results in which the yield was 66 % and a ratio of *syn/anti* was 78/22 were obtained.

#### <Example 6>

In accordance with the following reaction formulae,  $\gamma$ -lactams (12) were synthesized from the product obtained in Example 5:

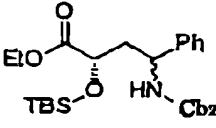


1) A CH<sub>2</sub>Cl<sub>2</sub> (0.6 ml) solution of the above-described product (10) (31.3 mg, 0.08 mmol) was added with a CH<sub>2</sub>Cl<sub>2</sub> (0.2 ml) solution of 2,6-lutidine (12.0 mg, 0.114 mmol) and a CH<sub>2</sub>Cl<sub>2</sub> solution of tert-butyl dimethyl silyl trifluoromethane sulfonate: TBDMSOTf (27.8 mg, 0.105 mmol) at a temperature of 0°C.

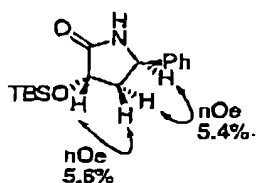
A reaction mixture was stirred for 10 hours at room temperature.

After the resultant reaction mixture was added with water, it was subjected to extraction by using CH<sub>2</sub>Cl<sub>2</sub> and, then, the resultant organic phase

was rinsed and, then, dried and, thereafter, a solvent therein was evaporated. The resultant crude product was purified by using silica gel chromatography, to thereby obtain 37.9 mg (with a yield of 92 %) of a next compound (11).


**4-Benzyloxycarbonylamino-2-(*tert*-butyl-dimethyl-silyloxy)-4-phenyl-butyric acid ethyl ester (11, diastereomer mixture):**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = *syn*: -0.03 (s, 3H), 0.02 (s, 3H), 0.90 (s, 9H), 1.15-1.27 (m, 3H), 2.00-2.35 (m, 2H), 3.90-4.30 (m, 3H), 4.80-5.15 (m, 3H), 5.50 (brs, 1H), 7.15-7.40 (m, 10 H); *anti*: (distinguishable peak)  $\delta$  = -0.02 (s, 3H), 0.03 (s, 3H), 5.62 (brd, 1H,  $J = 7.7$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) *syn*:  $\delta$  = -5.4, -5.0, 14.0, 18.1, 25.7, 41.0, 52.9, 61.0, 66.6, 70.3, 126.4, 127.4, 128.0, 128.1, 128.4, 128.6, 136.4, 141.8, 155.3, 173.2; *anti*: (distinguishable peak) -5.0, 14.1, 41.8, 52.3, 69.8, 126.0, 127.3, 128.6, 142.2, 155.6, 173.1; IR (neat) 3343, 2940, 1720, 1518, 1254, 1131, 1038, 839, 781, 699 $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{26}\text{H}_{38}\text{NO}_5\text{Si}$   $[\text{M}+\text{H}]^+$ , 472.2519. Found 472.2508.

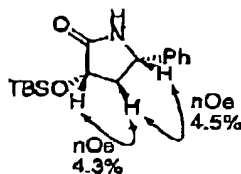
2) An AcOEt (2.0 ml) solution of the above-described product (11) (21.4 mg, 0.454 mmol) was added with AcOH (16.8 mg, 0.0272 mmol) and a 5 % Pd/C (9.7 mg, 10 % by mol) at room temperature. After an argon gas in the atmosphere of the resultant mixture was replaced with an  $\text{H}_2$  gas, the mixture was stirred for 11 hours, to thereby obtain a next compound (12) (13.4 mg, quantitative yield). A diastereomer (12) can be separated by using silica gel chromatography.



(3S, 5R)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenylpyrrolidin-2-one (12-major):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )

$\delta = 0.14$  (s, 3H),  $0.16$  (s, 3H),  $0.91$  (s, 9H),  $2.21$  (ddd, 1H,  $J = 5.1, 7.1, 13.2$  Hz),  $2.46$  (ddd, 1H,  $J = 5.1, 7.5, 13.2$  Hz),  $4.38$  (dd, 1H,  $J = 5.1, 7.1$  Hz),  $4.83$  (dd, 1H,  $J = 5.0, 7.5$  Hz),  $6.02$  (brs, 1H),  $7.20$ - $7.43$  (m, 5H);  $^{13}\text{C}$  NMR

( $\text{CDCl}_3$ )  $\delta = -5.1, -4.5, 18.3, 25.8, 41.5, 55.1, 69.9, 125.5, 127.9, 129.0, 142.1, 176.3$ ; IR (neat)  $3226, 2927, 2892, 2855, 1715, 1496, 1471, 1331, 1253, 1151, 1091, 1028, 963, 880, 839, 780, 699$   $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{16}\text{H}_{26}\text{NO}_2\text{Si}$   $[\text{M}+\text{H}]^+$ , 292.1733. Found 292.1733.;



(3S, 5S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenylpyrrolidin-2-one (12-minor):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta = 0.15$

(s, 3H),  $0.20$  (s, 3H),  $0.91$  (s, 9H),  $1.94$  (dt, 1H,  $J = 9.2, 12.6$  Hz),  $2.75$ - $2.87$  (m, 1H),  $4.42$  (dd, 1H,  $J = 7.9, 9.2$  Hz),  $4.53$  (dd, 1H,  $J = 6.2, 8.6$  Hz),  $5.76$  (brs, 1H),  $7.30$ - $7.40$  (m, 5H);  $^{13}\text{C}$  NMR

( $\text{CDCl}_3$ )  $\delta = -5.1, -4.5, 118.3, 25.8, 42.0, 53.9, 70.8, 126.1, 128.2, 128.9, 176.0$ ; IR (neat)  $3220, 2936, 2858, 2359, 1717, 1463, 1330, 1247, 1151, 882, 838, 781, 698$   $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{16}\text{H}_{26}\text{NO}_2\text{Si}$   $[\text{M}+\text{H}]^+$ , 292.1733. Found 292.1736.;

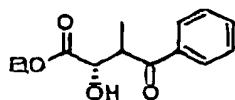
#### <Example 7>

A reaction was performed in a same manner as in Example 1 except that various types of enecarbamates shown in Table 10 as enamides represented by the above-described formula (2) were used. In Table 5, yield (%), a syn/anti ratio, and ee (%) of a reaction product are shown. Identification values of 7-1/7-2, 7-3/7-4, 7-5/7-6 and 7-7/7-8 of the reaction products are also shown.

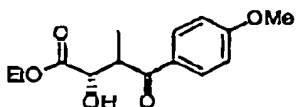
From the results of this reaction, it was confirmed that an anti-adduct and a syn-adduct were obtained from an E-body and a Z-body at high diastereoselectivity and high enantioselectivity, respectively.

**Table 5**

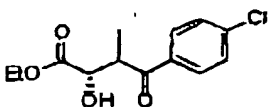
No.	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup> ·R <sup>5</sup>	Yield (%)	Syn/anti	ee (%)
7-1	BnO	Ph	Me, H (E)	83	1/99	98
7-2	BnO	Ph	H, Me (Z)	82	98/2	98
7-3	BnO	4-MeO-Ph	Me, H (E)	96	2/98	98
7-4	BnO	4-MeO-Ph	H, Me (Z)	97	98/2	98
7-5	EtO	4-MeO-Ph	Me, H (E)	82	3/97	96
7-6	EtO	4-MeO-Ph	H, Me (Z)	96	99/1	98
7-7	BnO	4-Cl-C <sub>6</sub> H <sub>4</sub>	Me, H (E)	85	2/98	98
7-8	BnO	4-Cl-C <sub>6</sub> H <sub>4</sub>	H, Me (Z)	79	99/1	98



**(2S)-2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester** (*syn/anti* mixture):  $^1\text{H}$  NMR *syn* ( $\text{CDCl}_3$ )  $\delta$  = 1.26 (t, 3H,  $J$  = 7.0 Hz), 1.29 (d, 3H,  $J$  = 7.0 Hz), 3.28 (br, 1H), 3.93 (dq, 1H,  $J$  = 4.2, 7.0 Hz), 4.25 (q, 2H,  $J$  = 7.0 Hz), 4.58 (d, 1H,  $J$  = 4.2 Hz), 7.40-7.65 (m, 3H), 7.90-8.05 (m, 2H); *anti* ( $\text{CDCl}_3$ )  $\delta$  = 1.20 (t, 3H,  $J$  = 7.1 Hz), 1.36 (d, 3H,  $J$  = 7.3 Hz), 3.61 (d, 1H,  $J$  = 8.3 Hz), 3.98 (dq, 1H,  $J$  = 4.6, 7.1 Hz), 4.10-4.25 (m, 2H), 4.39 (dd, 1H,  $J$  = 4.6, 8.3 Hz), 7.40-7.65 (m, 3H);  $^{13}\text{C}$  NMR *syn* ( $\text{CDCl}_3$ )  $\delta$  = 12.1, 14.0, 44.3, 61.9, 71.6, 128.4, 128.7, 133.3, 135.7, 173.1, 201.6; *anti* ( $\text{CDCl}_3$ )  $\delta$  = 14.0, 14.1, 44.0, 61.5, 73.1, 128.3, 128.7, 133.4, 135.9, 173.1; IR (neat) *syn* 3480, 3063, 2978, 2936, 1734, 1678, 1596, 1579, 1449, 1369, 1217, 1133, 1062, 1023, 1001, 975, 952, 862, 794, 708; *anti* 3481, 3059, 2981, 2941, 1738, 1685, 1588, 1454, 1372, 1255, 1209, 1144, 1092, 1024, 973, 701  $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{13}\text{H}_{17}\text{O}_4$   $[\text{M}+\text{H}]^+$ , 237.1127. Found 237.1118; HPLC, Daicel Chiralcel AS + ADH + AD, hexane/*i*PrOH = 4/1, flow rate = 0.5 mL/min:  $t_R$  = 46.7 min (2S, 3S),  $t_R$  = 50.6 min (2R, 3R),  $t_R$  = 54.3 min (2S, 3R),  $t_R$  = 61.9 min (2R, 3S).



**(2S)-2-Hydroxy-4-(4-methoxy-phenyl)-3-methyl-4-oxo-butyric acid ethyl ester** (*syn/anti* mixture):  $^1\text{H}$  NMR *syn* ( $\text{CDCl}_3$ )  $\delta$  = 1.28 (t, 3H,  $J$  = 7.1 Hz), 1.29 (d, 3H,  $J$  = 7.1 Hz), 3.35 (br, 1H), 3.84-3.96 (m, 4H), 4.27 (q, 2H,  $J$  = 7.1 Hz), 4.58 (t, 1H,  $J$  = 4.2 Hz), 6.96 (apparent d, 2H,  $J$  = 9.0 Hz), 7.30-7.45 (m, 5H), 7.95 (apparent d, 2H,  $J$  = 8.8 Hz); *anti* ( $\text{CDCl}_3$ )  $\delta$  = 1.19 (t, 3H,  $J$  = 7.1 Hz), 1.36 (d, 3H,  $J$  = 7.3 Hz), 3.75 (d, 1H,  $J$  = 9.3 Hz), 3.88 (s, 3H), 3.94 (dq, 1H,  $J$  = 4.6, 7.3 Hz), 4.15 (apparent dq, 2H,  $J$  = 3.2, 7.1 Hz), 4.36 (dd, 1H,  $J$  = 4.6, 9.3 Hz), 6.92-6.99 (m, 2H), 7.90-7.97 (m, 2H);  $^{13}\text{C}$  NMR *syn* ( $\text{CDCl}_3$ )  $\delta$  = 12.3, 14.0, 43.7, 55.4, 61.8, 71.7, 113.9, 128.5, 130.7, 163.7, 173.1, 200.4; *anti* ( $\text{CDCl}_3$ )  $\delta$  = 14.0, 14.6, 43.2, 55.5, 61.4, 73.4, 113.9, 128.7, 130.8, 163.8, 173.2, 201.9; IR (neat) *syn* 3477, 2979, 2935, 2850, 1730, 1670, 1600, 1573, 1510, 1463, 1420, 1308, 1261, 1173, 1125, 1027, 976, 843, 770, 604; *anti* 3478, 2979, 2941, 2843, 1738, 1671, 1599, 1580, 1510, 1457, 1419, 1370, 1308, 1257, 1216, 1172, 1092, 1026, 974, 841  $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{14}\text{H}_{19}\text{O}_5$   $[\text{M}+\text{H}]^+$ , 267.1232. Found 267.1232; HPLC, Daicel Chiralcel ADH, hexane/*i*PrOH = 4/1, flow rate = 0.2 mL/min:  $t_R$  = 60.5 min (2R, 3R),  $t_R$  = 65.4 min (2S, 2S),  $t_R$  = 75.2 min (2R, 3S),  $t_R$  = 78.9 min (2S, 3R).



**(2S)-4-(4-Chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-butyric acid ethyl ester** (*syn/anti* mixture):  $^1\text{H}$  NMR *syn* ( $\text{CDCl}_3$ )  $\delta$  = 1.26 (t, 3H,  $J$  = 7.0 Hz), 1.28 (d, 3H,  $J$  = 7.0 Hz), 3.27 (brs, 1H), 3.87 (dq, 1H,  $J$  = 4.4, 7.0 Hz), 4.25 (q, 2H,  $J$  = 7.0 Hz), 4.55 (d, 1H,  $J$  = 4.4 Hz), 7.40-7.55 (m, 2H), 7.84-7.97 (m, 2H); *anti* ( $\text{CDCl}_3$ )  $\delta$  = 1.21 (t, 3H,  $J$  = 7.1 Hz), 1.34 (d, 3H,  $J$  = 7.1 Hz), 3.53 (d, 1H,  $J$  = 8.2 Hz), 3.91 (dq, 1H,  $J$  = 5.0, 7.1 Hz), 4.08-4.24 (m, 2H), 4.38 (dd, 1H,  $J$  = 5.0, 8.2 Hz), 7.42-7.52 (m, 2H), 7.80-7.95 (m, 2H);  $^{13}\text{C}$  NMR *syn* ( $\text{CDCl}_3$ )  $\delta$  = 12.1, 14.0, 44.4, 62.0, 71.5, 129.0, 129.8, 134.1, 139.7, 173.1, 200.3; *anti* ( $\text{CDCl}_3$ )  $\delta$  = 13.9, 14.0, 44.1, 61.6, 73.0, 129.0, 129.8, 134.3, 139.9, 173.0, 201.8; IR (neat) *syn* 3485, 2982, 2938, 1730, 1682, 1589, 1571, 1488, 1455, 1401, 1217, 1132, 1092, 1013, 977, 843, 758, 692, 533, 478; *anti* 3478, 3092, 2982, 2935, 1738, 1686, 1589, 1455, 1402, 1255, 1208, 1144, 1092, 1022, 976, 842, 751, 527  $\text{cm}^{-1}$ ; HRMS (FAB); Exact mass calcd for  $\text{C}_{13}\text{H}_{16}\text{ClO}_4$   $[\text{M}+\text{H}]^+$ , 271.0737. Found 271.0745; HPLC, Daicel Chiralcel AS, hexane/*i*PrOH = 4/1, flow rate = 0.5 mL/min:  $t_R$  = 15.1 min (2S, 3S),  $t_R$  = 16.6 min (2S, 3R),  $t_R$  = 21.4 min (2R, 3S),  $t_R$  = 23.9 min (2R, 3R).



**<Example 8>**

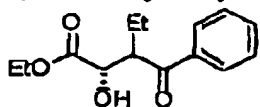
A reaction was performed in a same manner as in Example 7 except that various types of enecarbamates as shown in Table 6 were used. In Table 6, yield (%), a syn/anti ratio, and ee (%) of a reaction product are shown. Identification values of 8-1/8-2 and 8-3/8-4 of the reaction products are also shown.

It was confirmed that, in a same manner as in Example 7, an anti-adduct and a syn-adduct were obtained from an E-body and a Z-body at high diastereoselectivity and high enantioselectivity, respectively.

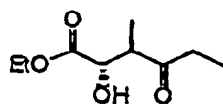
**Table 6**

No.	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup> -R <sup>5</sup>	Yield (%)	Syn/anti	ee (%)
8-1	BnO	Ph	Et, H (E)	90	1/99	98
8-2	BnO	Ph	H, Et (Z)	92	99/1	98
8-3	BnO	Et	Me, H (E)	83	3/97	97
8-4	BnO	Et	H, Me (Z)	89	92/8	98

(2*S*)-3-Benzoyl-2-hydroxy-pentanoic acid ethyl ester ( *syn/anti* mixture): <sup>1</sup>H NMR *syn* (CDCl<sub>3</sub>) δ = 0.93 (t, 3H, *J* = 7.5 Hz), 1.19 (t, 3H,



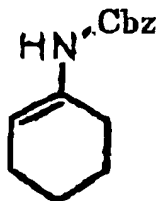
*J* = 7.1 Hz), 1.70-2.05 (m, 2H), 3.18 (brs, 1H), 3.83 (dt, 1H, *J* = 5.3, 8.3 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 4.51 (d, 1H, *J* = 5.3 Hz), 7.42-7.54 (m, 2H), 7.54-7.62 (m, 1H), 7.90-8.02 (m, 2H); *anti* (CDCl<sub>3</sub>) δ = 1.04 (t, 3H, *J* = 7.6 Hz), 1.15 (t, 3H, *J* = 7.1 Hz), 1.80-1.95 (m, 2H), 3.70 (d, 1H, *J* = 9.5 Hz), 3.83 (dt, 1H, *J* = 4.2, 7.1 Hz), 4.09 (q, 2H, *J* = 7.1 Hz), 4.43 (dd, 1H, *J* = 4.2, 9.5 Hz), 7.46-7.52 (m, 2H), 7.56-7.63 (m, 1H), 7.88-7.95 (m, 2H); <sup>13</sup>C NMR *syn* (CDCl<sub>3</sub>) δ = 12.0, 13.9, 21.3, 51.2, 61.9, 71.1, 128.3, 128.6, 133.2, 137.0, 173.6, 201.5; *anti* (CDCl<sub>3</sub>) δ = 12.0, 13.9, 22.3, 50.1, 61.4, 71.3, 128.3, 128.7, 133.5, 136.6, 173.4, 203.9; IR (neat) *syn* 3477, 2972, 2876, 1738, 1675, 1596, 1447, 1372, 1255, 1220, 1118, 1023, 931, 849, 779, 701; *anti* 3485, 3062, 2966, 2941, 2875, 1738, 1682, 1596, 1579, 1448, 1368, 1268, 1208, 1134, 1100, 1028, 914, 849, 785, 699 cm<sup>-1</sup>; HRMS (FAB); Exact mass calcd for C<sub>14</sub>H<sub>19</sub>O<sub>4</sub> [M+H]<sup>+</sup>, 251.1283. Found 251.1277.; HPLC, Daicel Chiralcel AS, hexane/*i*PrOH = 4/1, flow rate = 0.5 mL/min: *t*<sub>R</sub> = 13.7 min (2*S*, 3*S*), *t*<sub>R</sub> = 15.3 min (2*S*, 3*R*), *t*<sub>R</sub> = 17.6 min (2*R*, 3*R*), *t*<sub>R</sub> = 23.1 min (2*R*, 3*S*).



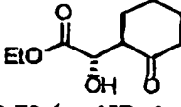
(2*S*)-2-Hydroxy-3-methyl-4-oxo-hexanoic acid ethyl ester ( *syn/anti* mixture): <sup>1</sup>H NMR *syn* (C<sub>6</sub>D<sub>6</sub>) δ = 0.89 (t, 3H, *J* = 7.1 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 1.97-2.08 (m, 2H), 2.70 (dq, 1H, *J* = 4.9, 7.2 Hz), 3.39 (d, 1H, *J* = 6.7 Hz), 3.80-4.00 (m, 2H), 4.11 (dd, 1H, *J* = 4.9, 6.7 Hz); *anti* (C<sub>6</sub>D<sub>6</sub>) δ = 0.87 (t, 3H, *J* = 7.1 Hz), 0.93 (t, 3H, *J* = 7.3 Hz), 1.02 (d, 3H, *J* = 7.2 Hz), 1.95-2.22 (m, 2H), 2.65 (dq, 1H, *J* = 4.4, 7.2 Hz), 3.05-3.23 (m, 1H), 3.80-4.00 (m, 2H), 4.38-4.47 (m, 1H); <sup>13</sup>C NMR *syn* (CDCl<sub>3</sub>) δ = 7.58, 12.8, 14.0, 34.6, 49.4, 61.3, 73.0, 173.5, 211.3; *anti* (C<sub>6</sub>D<sub>6</sub>) δ = 7.7, 11.0, 14.0, 34.0, 49.5, 61.6, 71.7, 173.7, 209.9; IR (neat) *syn* 3484, 2981, 2940, 1739, 1716, 1459, 1409, 1375, 1268, 1209, 1108, 1066, 1025, 975, 862, 808, 748; *anti* 3488, 2981, 2940, 1733, 1716, 1459, 1373, 1218, 1145, 1025, 977, 862, 800, 752 cm<sup>-1</sup>; HRMS (FAB); Exact mass calcd for C<sub>9</sub>H<sub>17</sub>O<sub>4</sub> [M+H]<sup>+</sup>, 189.1127. Found 189.1120.;

#### <Example 9>

A reaction was performed in a same manner as in Example 7 except that an enecarbamate represented by the following formula as an enamide:



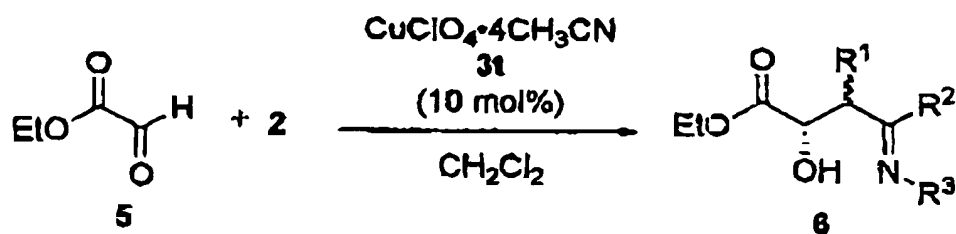
Thus, a next compound was obtained at a yield of 85 % with a syn/anti of 16/84 and 94 ee (%).

 (1S)-Hydroxy-(2-oxo-cyclohexyl)-acetic acid ethyl ester (*syn/anti* mixture):  $^1\text{H}$  NMR *anti* ((1S, 1'R), tentatively assignment) ( $\text{C}_6\text{D}_6$ )  $\delta$  = 0.95 (t, 3H,  $J$  = 7.1 Hz), 0.94-1.20 (m, 2H), 1.30-1.42 (m, 2H), 1.56-1.84 (m, 3H), 2.02-2.12 (m, 1H), 2.60-2.70 (m, 1H), 3.35 (d, 1H,  $J$  = 7.2 Hz), 3.84 (dd, 1H,  $J$  = 3.2, 7.2 Hz), 4.02 (dq, 2H,  $J$  = 1.9, 7.1 Hz); distinguishable *syn* peaks  $\delta$  = 0.88 (t, 3H,  $J$  = 7.1 Hz), 2.12-2.21 (m, 1H), 2.48-2.57 (m, 1H), 2.94 (d, 1H,  $J$  = 5.0 Hz), 4.60 (dd, 1H,  $J$  = 3.2, 5.0 Hz);  $^{13}\text{C}$  NMR *anti* ( $\text{CDCl}_3$ )  $\delta$  = 14.1, 24.8, 26.9, 30.1, 42.0, 53.7, 61.6, 71.1, 173.4, 211.2; distinguishable *syn* peaks  $\delta$  = 14.2, 24.6, 27.1, 41.9, 53.8, 61.7, 69.2, 173.6, 210.4; HRMS (FAB); Exact mass calcd for  $\text{C}_{10}\text{H}_{17}\text{O}_4$  [ $\text{M}+\text{H}$ ] $^+$ , 201.1127. Found 201.1127.;

#### <Example 10>

A reaction was performed in a same manner as in Example 7 except that an enamide (2) having an  $\alpha$ -substituent as shown in Table 7 was used. The results are also shown in Table 7.

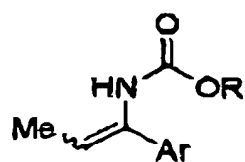
Table 7



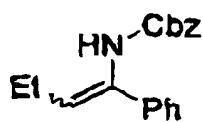
entry	2	product	yield (%) <sup>a</sup>	syn/anti <sup>b</sup>	ee (%) <sup>c</sup>
1	2fE	7f	83	1/99	98
2 <sup>d</sup>	2fE <sup>e</sup>	7f	93	1/99	97
3 <sup>d</sup>	2fE'	7f	95	1/99	98
4	2fZ	7f	82	98/2	98
5	2fZ <sup>e</sup>	7f	93	98/2	98
6	2fZ'	7f	98	98/2	98
7	2gE	7g	96	2/98	98
8	2gZ	7g	97	98/2	98
9	2hE	7g	82	3/97	96
10	2hZ	7g	96	99/1	98
11	2iE	7i	85	2/98	98
12	2iZ	7i	79	99/1	98
13	2jE <sup>g</sup>	7j	58	1/99	98
14	2jZ	7j	92	99/1	98
15 <sup>d</sup>	2kE	7k	83	3/97 <sup>h</sup>	97
16 <sup>d</sup>	2kZ	7k	89	92/8 <sup>h</sup>	98
17	2l	7l	85	16/84 <sup>h</sup>	94

<sup>a</sup> Isolated yield of ketone product. <sup>b</sup> Determined by HPLC. <sup>c</sup> Ee of the major diastereomer, determined by HPLC.

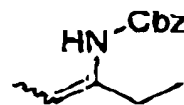
<sup>d</sup> -20 °C. <sup>e</sup> 1 mol% of catalyst was used. 0.1 mol% of catalyst was used. <sup>g</sup> 1 (1.0 eq.) and 2 (2.0 eq.) were used. <sup>h</sup> Determined by NMR analysis.



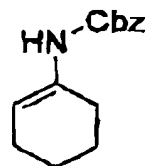
2f: Ar = Ph, R = Bn  
 2g: Ar = PMP, R = Bn  
 2h: Ar = PMP, R = Et  
 2i: Ar = PCP, R = Bn



2j



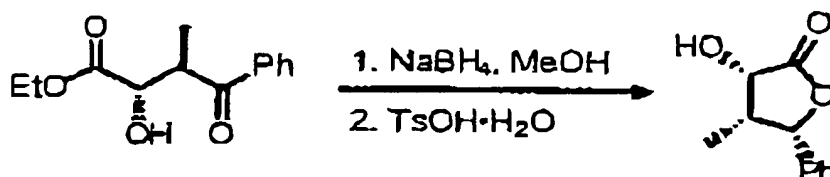
2k



2l

## &lt;Example 11&gt;

From the reaction product obtained in Example 7, an optically active  $\alpha$ -hydroxy- $\gamma$ -lactone was synthesized in accordance with the following reaction formulae:

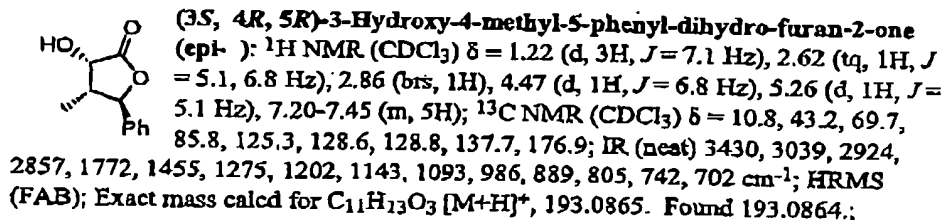
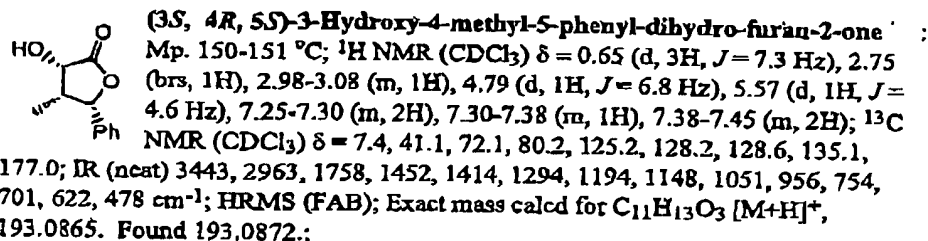


Namely, MeOH (1.0 ml) of the anti-body (45.6 mg, 0.193 mmol) of the reaction product was added with NaBH<sub>4</sub> (14.6 mg, 0.39 mmol) at 0°C, stirred for 10 minutes, added with acetone, stirred further for 5 minutes and, then, added with a saturated aqueous solution of NH<sub>4</sub>Cl.

The resultant mixture was subjected to extraction by using CH<sub>2</sub>Cl<sub>2</sub>, dried and, then, a solvent was evaporated. Thereafter, the resultant CH<sub>2</sub>Cl<sub>2</sub> solution (1 ml) was added with TsOH·H<sub>2</sub>O and, then, stirred for 13.5 hours at room temperature.

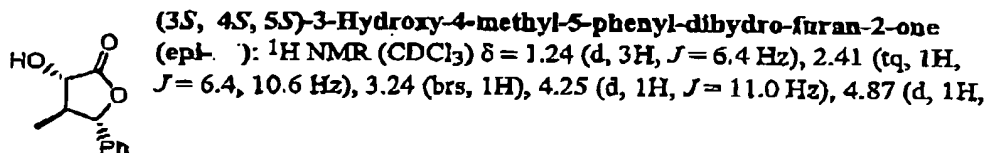
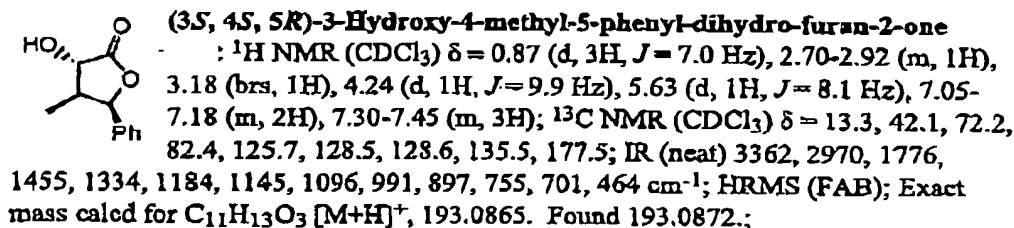
The resultant reaction product was added with a saturated aqueous solution of NaHCO<sub>3</sub>, subjected to extraction by using CH<sub>2</sub>Cl<sub>2</sub>, dried and, then, subjected to a solvent-evaporation treatment. The resultant crude product was purified by using silica gel chromatography. As a product, the lactone compound as shown in the above-described reaction formulae and an epi-body thereof (ratio: 55/45) were obtained as a diastereomer mixture in an amount of 19.8 mg at a yield of 53%.

Identification values of the products are shown below.



In a same manner as described above, by using the syn-body of the product in Example 7 as a raw material, a lactone compound and an epi-body thereof (ratio: 86/14) were obtained at a yield of 84 %.

Identification values of the products are shown below.

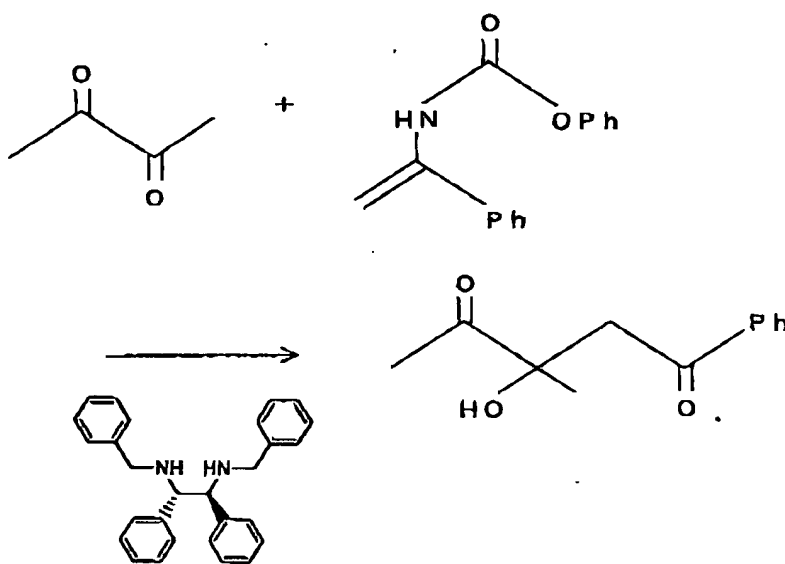


#### <Example 12>

A dichloromethane solution (2 ml) of  $\text{Ni}(\text{OTf})_2$  was added with a dichloromethane solution (3 ml) of chiral diamine (0.15 mmol) represented by the formula shown below in an argon atmosphere at room temperature and, then, stirred for 8 hours. After being cooled to 0°C, the resultant solution was added with a dichloromethane solution (2.5 ml) of diketone (1.5 mmol) and a dichloromethane solution (2.5 ml) of enamide (1.0 mmol) in succession. After being stirred for 48 hours, the resultant mixture was added with a 48 %

hydrobromic acid solution (0.5 ml) in drops, stirred for 5 minutes and, then, added with a saturated aqueous solution of sodium hydrogen carbonate. The resultant reaction solution was subjected to extraction using dichloromethane and the resultant organic phase was rinsed with water and, then, a saturated saline solution and, thereafter, dried on sodium sulfate anhydride and, then, concentrated under a reduced pressure, to thereby obtain a product of constitution. The thus-obtained product of constitution was purified by using silica gel chromatography, to thereby obtain hydroxydiketone at a yield of 77 % with an optical purity of 59 % ee.

When a reaction was performed under same conditions as described above except that  $\text{Cu}(\text{OTf})_2$  was used in place of  $\text{Ni}(\text{OTf})_2$ , hydroxydiketone was obtained at a yield of 52 % with an optical purity of 72 % ee.



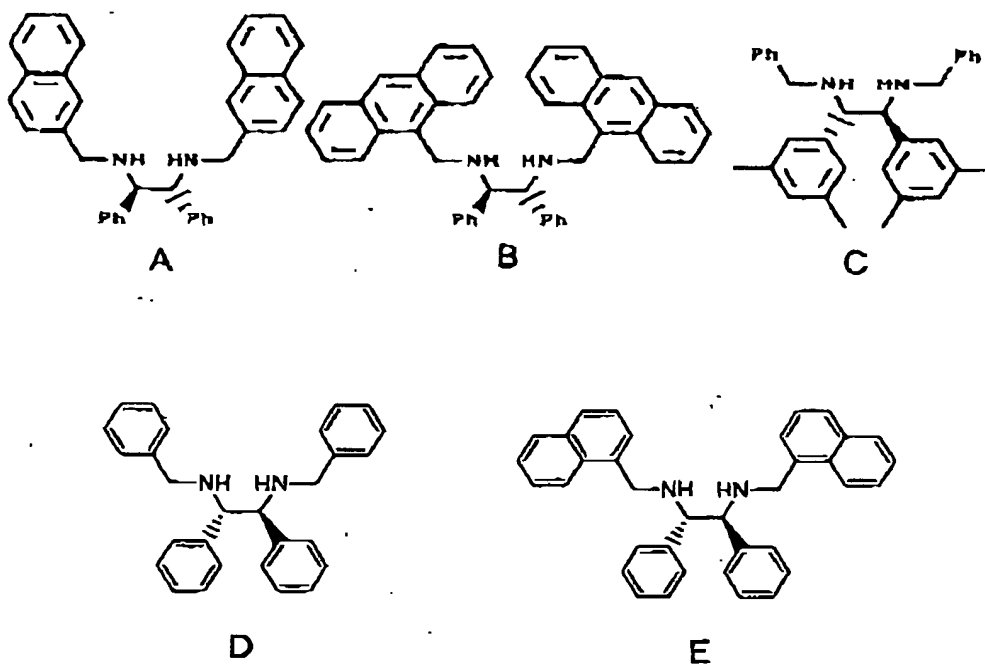
#### <Example 13>

A reaction was performed in a same manner as in Example 12, except for using a chiral catalyst system constituted by using  $\text{Ni}(\text{OTf})_2$  or  $\text{Cu}(\text{OTf})_2$  and various types of chiral diamine ligands (A, B, C, D, E). The results are shown in Table 8.

**Table 8**

entry	liganal	metal	yield (%)	ee (%)
1	A	Ni	30	83
2	A	Cu	70	40
3	B	Ni	23	70
4	B	Cu	61	58
5	C	Ni	24	81
6	C	Cu	62	33
7	D	Ni	67	75
8	D	Cu	70	49
9	E	Ni	37	80
10	E	Cu	61	62

10 % by mol was used in DCM. Reaction at 0°C.



<Example 14>



A reaction was performed in a same manner as in Example 12, except that  $\text{NiCl}_2$  and  $\text{AgOTf}$  of two equivalents thereof were used in place of  $\text{Ni}(\text{OTf})_2$ .

As a result, a hydroxydiketone was obtained at a yield of 85% and an optical purity of 57% ee. Further, when  $\text{AgOTf}$  of three equivalents thereof was used, the yield was 56% and the optical purity was 81% ee.

#### Industrial Applicability

As has been described above in detail, according to the present invention, there is provided a method of an enantioselective nucleophilic addition reaction to an aldehyde group which enables an asymmetric synthesis of an optically active  $\alpha$ -hydroxy- $\gamma$ -keto acid ester, an optically active  $\alpha$ -hydroxy- $\gamma$ -amino acid ester, an optically active hydroxydiketone or the like which is useful as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like. Then, according to the invention, high stereoselective reaction is made possible and, particularly in the case of an enecarbamate having an  $\alpha$ -1 substitution, high diastereoselectivity and enantioselectivity are realized. Further, there is provided a novel method for synthesizing an optically active  $\gamma$ -lactam or any one of  $\gamma$ -lactones.